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Duration of Increased Pulmonary Function Sensitivity to an Initial Ozone Exposure

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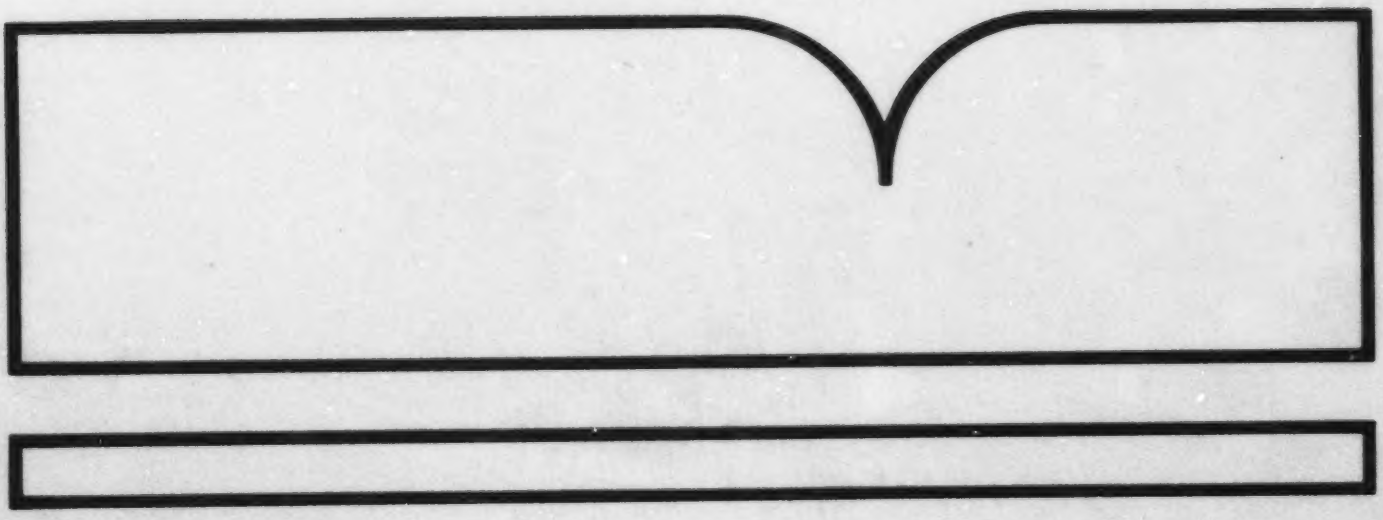

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16. ABSTRACT

The metabolic and pulmonary function effects were investigated in 6 non-smoking, young adults who were exposed for 2 hours (22°C WBGT) to: (1) Filtered air (FA), (2) 0.45 ppm ozone (DAY), and (3) Two days later to a second exposure to 0.45 ppm ozone exposure (DAY 2). The subjects alternated 20-minute periods of rest and 20-minute periods of bicycle ergometer exercise at a work load predetermined to elicit a VE of 27 L/min (BTPS). Functional residual capacity (FRC) was determined pre- and post-exposure. Forced vital capacity (FVC) was determined before and after exposure, as well as 5 minutes after each exerciseperiod. Heart rate was monitored throughout the exposure, and ventilatory minute volume (VE), oxygen uptake (V02), respiratory rate (fR), and tidal volume (VT) were measured during the last 2 minutes of each exercise period. There were no changes in any variable consequent to FA exposure. Both ozone exposures induced significant ($p < 0.05$) decrements in FVC, FEV-1, FEV-3, FEF 25-75%, and TLC. The decrements following the DAY 2 ozone exposure averaged 7.2% greater than those following the DAY 1 exposure.

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Duration of Increased Pulmonary Function Sensitivity to an Initial Ozone Exposure

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The metabolic and pulmonary function effects were investigated in six non-smoking young adults who were exposed for 2 hours (22° C WBGT) to: 1) filtered air (FA); 2) 0.45 ppm ozone (DAY1); and 3) two days later to a second exposure to 0.45 ppm ozone (DAY2). The subjects alternated 20-minute periods of rest and 20-minute periods of bicycle ergometer exercise at a workload predetermined to elicit a ventilatory minute volume ($\dot{V}_E$) of 27 L/min (BTPS). Functional residual capacity (FRC) was determined pre- and post-exposure. Forced vital capacity (FVC) was determined before and after exposure, as well as 5 minutes after each exercise period. Heart rate was monitored throughout the exposure, and $\dot{V}_E$, oxygen uptake ($\dot{V}_{O_2}$), respiratory rate (f_R), and tidal volume (V_T) were measured during the last 2 minutes of each exercise period. There were no changes in any variable consequent to FA exposure. Both ozone exposures induced significant ($P < 0.05$) decrements in FVC; $FEV_{1.0}$ (forced expiratory volume in 1 second); $FEV_{3.0}$ (forced expiratory volume in 3 seconds); FEF25-75% (average flow rate between 25% and 75% of FVC); and total lung capacity (TLC). The decrements following the DAY2 ozone exposure were significantly greater than following DAY1, and averaged 7.2 percentage points greater than those following the DAY1 exposure.

Introduction

Human Studies utilizing daily acute exposures to ozone have investigated the time required for development of desensitization to ozone,[1-4] the duration of the desensitization response,[5-7] and whether desensitization to one ozone concentration implies desensitization in general, to a higher concentration of ozone.[3] These studies have noted increased decrements in pulmonary functions and an increased number of symptoms reported by the subjects on the second day of ozone exposure.

No experiments have been designed to measure the persistence of this apparent increase in the responsiveness of the lung to ozone exposure after an initial exposure. There is evidence that increased responsivity does not persist for 7 days.[1,5] Investigations of repeated exposures to ozone or ozone in combination with a second pollutant[9,10] which have allowed a minimum of 7 days between exposures have found no difference in the pulmonary function responses of their subjects following the exposures. There are, however, various confounding factors in the above studies, *i.e.*, differences in temperature, humidity, exercise protocol, presence of other pollutants and the variable time between the O_3 exposures, *i.e.* from 7 days to several weeks. A repeated ozone exposure study[11] where the average time between exposures was 6.9 days showed no difference between the pulmonary function responses to ozone.

The purpose of this study was to investigate whether lung responsiveness to ozone after an initial exposure would persist for 48 hours. This was accomplished by exposing subjects twice to ozone with the ozone exposures separated by one day of non-exposure.

Methods

Six healthy young adults (5 women and 1 man) — 18-30 years of age and all non-smokers — served as subjects for this experiment (Table I). Our previous research has shown no difference between the pulmonary function response of men and women subjects exposed to equivalent environmental conditions at the same absolute workload and utilizing the same intermittent exercise protocol (unpublished manuscript). The purpose and attending risks and benefits of the experiment were verbally explained and given on a written form to each subject prior to his/her voluntary consent to participate. The protocol and procedures for this study were approved by the Committee on Activities Involving Human Subjects, of the University of California, Santa Barbara. Each potential subject was screened by medical history, resting 12-lead ECG, and a battery of clinical pulmonary function tests.

The subjects were exposed to each of the following conditions: 1) filtered air; 2) 0.45 ppm ozone (DAY1); and 3) two

TABLE I
Subject Characteristics (Mean ± SD) (n = 6)

	Age (years)	Weight (kg)	Height (cm)	BSA (m^2)	FVC (mL)	$FEV_{1.0}$ (mL)	$FEV_{1.0}/FVC$
Mean	21.2	66.8	172.7	1.79	4640	3835	0.828
± SE	±4.0	±9.9	±10.0	±0.18	±801	±666	±0.051

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TABLE II
Changes in FVC During Exposure[A]

	FA	DAY1	DAY2
Pre	4627 ±896	4648 ±839	4599 ±966
Min 40	4609 ±919	4636 ±922	4568 ±911
Min 75	4597 ±957	4402 ±928	4225[B,D] ±928
Min 110	4571 ±885	4197[B,D] ±1104	3879[C,D,E] ±1014

[A]Mean value in mL ± SD.
[B]< FA ($P < 0.05$).
[C]< DAY1 ($P < 0.05$).
[D]< Pre and Min 40 ($P < 0.05$).
[E]< Min 75 ($P < 0.05$).

days later a second exposure to 0.45 ppm ozone (DAY2). The exposures were carried out in a 1.75 × 1.75 × 2.24 m double-walled acrylic chamber. Inlet air was chemically and mechanically filtered prior to entering the chamber and was exhausted to the roof. The chamber air turnover time was approximately 2.5 min. Ozone was generated from 100% O_2 by two ultraviolet ozone generators (OREC) and was added to the chamber via the air intake duct. The chamber ozone concentration was monitored continuously by an ultraviolet absorption ozone analyzer (Dasibi, 1003-AH), which was periodically calibrated against a standard ozone photometer (Dasibi) by the California Air Resources Board (El Monte, Calif.). The mean environmental temperatures were 22.0°, 22.7°, and 23.1°C WBGT* for the FA, DAY1, and DAY2 exposures, respectively. The mean ozone concentration on DAY1 and DAY2 was identical (0.449 ppm).

During each 2-hour exposure the subjects alternated 20-minute periods of rest ($n = 3$) and 20-minute periods of bicycle exercise ($n = 3$) at a work load sufficient to yield a ventilatory minute volume of approximately 27 L/min (BTPS). The appropriate work load for each subject was determined in a practice session prior to the first experiment. The work loads ranged from 200-450 kgm/min, depending on the physical fitness status of the subject.

Functional residual capacity (FRC) was determined prior to and immediately after each exposure by the helium dilution method. Two forced vital capacity (FVC) maneuvers were recorded before the exposure began and also 5 minutes after each exercise period. Pulmonary functions were performed on W.E. Collins 13.5-L spirometers with the subject in the standing position. The following were calculated from the best FVC and FRC recordings: forced expiratory volume in 1 and 3 seconds ($FEV_{1.0}$, $FEV_{3.0}$); average flow from 25% to 75% of the FVC maneuver (FEF25-75%); residual volume (RV); and total lung capacity (TLC). All volumes were corrected to BTPS.

*WBGT = wet bulb globe temperature
$= 0.3\ T_{\text{wet bulb}} + 0.7\ T_{\text{globe or dry bulb}}$

Ventilatory minute volume ($\dot{V}_E$) was measured during the last 2 minutes of each exercise period by directing the subject's expired air through a Parkinson-Cowan gas meter. Aliquots of expired air were analyzed by gas chromatography (Quintron, H-3) for O_2 and CO_2 content, and these data were used to calculate oxygen uptake ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) via standard open-circuit technique. Heart rate was monitored throughout each exposure and was recorded at 5-minute intervals during the exercise periods. Following each exposure, the subject completed a checklist reporting any symptoms experienced during the exposure.

Data were analyzed by two-factor analysis of variance with repeated measures across time and pollutant. Where significant differences were found ($P < 0.05$), a further analysis of simple main effects, followed by a Tukey test, was employed to determine significant factor interactions.

Results

There were no significant differences in $\dot{V}_E$, $\dot{V}_{O_2}$, or $\dot{V}_{CO_2}$ across either time or exposure. The mean minute ventilation for all exposures was 27.8 L/min (BTPS). The total number of symptoms reported on DAY1 (48) and DAY2 (46) was similar, although on both days more symptoms were reported than following the FA exposure.

There were no significant differences among the pre-exposure measurements of pulmonary function for the three exposures, nor were there any significant changes consequent to the FA exposure. There was a statistically significant decrement in FVC (Table II) at minute 110 of the DAY1 exposure. The decrement in FVC on DAY2 became significant at minute 75, and was significantly larger at minute 110 than on DAY1. The decrements in FVC following both O_3 exposures were significantly different from the minute 110 measurement of the FA exposure. $FEV_{1.0}$ (Table III) was significantly decreased from the pre-exposure value at minute 75 of both the DAY1 and DAY2 exposures, with the DAY2 value significantly smaller than at minute 75 of the

TABLE III
Changes in $FEV_{1.0}$ During Exposure[A]

	FA	DAY1	DAY2
Pre	3893 ±642	3863 ±655	3794 ±715
Min 40	3804 ±625	3714 ±708	3711 ±654
Min 75	3770 ±593	3719[D] ±850	3409[B,D] ±661
Min 110	3723 ±517	3349[B,D,E] ±939	2929[B,C,D,F] ±797

[A]Mean value in mL ± SD.
[B]< FA ($P < 0.05$)
[C]< DAY1 ($P < 0.05$).
[D]< Pre ($P < 0.05$).
[E]< Min 40 ($P < 0.05$).
[F]< Min 40 and Min 75 ($P < 0.05$).

FA exposure. At min 110, $FEV_{1.0}$ was significantly reduced for both DAY1 and DAY2 exposures compared with the FA exposure, and the DAY2 decrement was significantly larger than that on DAY1. The decrement in $FEV_{3.0}$ (Table IV) became significant at min 110 of the DAY1 exposure, while it was significantly decreased at minute 75 of the DAY2 exposure. $FEV_{3.0}$ was significantly smaller at minute 75 of the DAY2 exposure than at the same time of both the FA and DAY1 exposures. The minute 110 measurements on DAY1 and DAY2 of $FEV_{3.0}$ were significantly smaller than the FA value. Decrements in FEF25-75% (Table V) became significant at minute 75 of both the DAY1 exposure and the DAY2 exposure. At minute 110, FEF25-75% measured on DAY2 was significantly smaller than both DAY1 and FA and DAY1 was less than the FA exposure.

There were no significant changes in FRC or ERV. The post-exposure values for RV were significantly larger than the pre-exposure values. The post-exposure measurements of TLC for both DAY1 and DAY2 were significantly less than the pre-exposure values, as well as significantly less than the FA post-exposure value.

Discussion

Increased decrements in pulmonary function on the second consecutive day of O_3 exposure have been observed by several investigators.[1,2,5-7,12] In one study, our laboratory[5] has found that the decrements in FVC, $FEV_{1.0}$, and FEF25-75% averaged, respectively, 4.8, 5.3 and 7.3 percentage points greater following the second exposure than the first for 24 subjects who performed intermittent exercise for 2 hours while exposed to 0.42 ppm O_3. In another study,[2] we observed in 7 subjects that the decrement in $FEV_{1.0}$ was 7.9 percentage points greater on the second day of exposure to 0.40 ppm O_3 than on the first day. Other investigators[7] exposed 11 subjects to 0.47 ppm O_3 for 2 hours on consecutive days and observed that the decrement in $FEV_{1.0}$ was 11.2 percentage points greater following the second exposure compared to those changes following the first. In a separate study from the same lab,[12] however, they reported an increase in the decrement in $FEV_{1.0}$ of only 1.4 percentage points on the second day of exposure to 0.40 ppm O_3 in 6 subjects. These studies all utilized consecutive daily exposures in their design. We found decrements following the DAY2 exposure were 6.0, 9.5 and 11.8 percentage points larger in FVC, $FEV_{1.0}$ and FEF25-75%, respectively, than following the DAY1 exposure. The size of the decrement increase on DAY2 compared to DAY1 is consistent with the above studies,[2,5,7,12] taking into account the exercise load, exposure duration and concentration of O_3 used — although the time period between the two O_3 exposures was approximately 24 hours greater in the present study.

TABLE IV
Changes in $FEV_{3.0}$ During Exposure[A]

	FA	DAY1	DAY2
Pre	4559 ±844	4698 ±914	4481 ±973
Min 40	4559 ±898	4543 ±876	4497 ±859
Min 75	4528 ±913	4351 ±944	3886[B,C,D] ±917
Min 110	4525 ±876	4070[B,D] ±1200	3783[B,D] ±1001

[A]Mean value in mL ± SD.
[B]< FA ($P < 0.05$).
[C]< DAY1 ($P < 0.05$).
[D]< Pre and Min 40 ($P < 0.05$).

TABLE V
Changes in FEF25-75% During Exposure[A]

	FA	DAY1	DAY2
Pre	4.37 ±0.92	4.14 ±0.69	3.82 ±0.67
Min 40	3.90 ±0.58	3.87 ±0.60	3.65 ±0.55
Min 75	3.93 ±0.58	3.47[C] ±0.93	3.30[C] ±0.71
Min 110	3.96 ±0.46	3.33[D] ±0.92	2.66[B,E] ±0.85

[A]Mean value in L/sec ± SD.
[B]< FA and DAY1 ($P < 0.05$).
[C]< Pre ($P < 0.05$).
[D]< Pre and Min 40 ($P < 0.05$).
[E]< Pre and Min 40 ($P < 0.05$).

The primary finding of this study was an increased pulmonary function response to a second O_3 challenge given 48 hours after the initial exposure. The decrements in the various pulmonary functions following the DAY2 exposure were, on the average, 7.2 percentage points larger than those following the DAY1 exposure.

Sensitization of irritant receptors is thought to be a major cause of the decrements in pulmonary function which occur consequent to O_3 exposure, as well as the increased decrements observed following a second consecutive O_3 exposure, although other mechanisms have also been suggested. It has been shown that the increased response to histamine challenge following O_3 exposure did not persist for 24 hours post-exposure.[13,14] Two separate studies[6,15] have reported that the response to bronchial challenge (metacholine and histamine) following each of several consecutive O_3 exposures was less than following the initial exposure. This fact suggests that some factor in addition to sensitization of irritant receptors is responsible for the increased pulmonary function response following a second O_3 exposure. Another possible mechanism thought to be responsible for the pulmonary function response following O_3 exposure is a decrease in mucus layer thickness. Following a single O_3 exposure to 0.8 ppm O_3, decreased mucus secretion occurs in excised rat tracheal explants and persists for 5 to 10 days before returning to the pre-challenge level.[16] Other investigators[17,18] have shown a decrease in oxygen consumption of lung homogenates after an initial exposure to O_3 followed by an increase after approximately 3 days, persisting for the

remaining exposure days and disappearing within 7 days after the final O_3 exposure.

None of these mechanisms, however, provides a satisfactory explanation of our finding of increased pulmonary function responsiveness following the DAY2 exposure compared to the DAY1 exposure. The time course of the suggested mechanisms does not agree with a duration of hypersensitivity that lasts for 2 days. While sensitization of irritant receptors probably is responsible for a part of the increased decrements in pulmonary function observed following the DAY2 exposure, it appears that some other mechanism, as yet unknown, also is involved, a mechanism that increases the responsiveness of the lung to O_3 exposure for at least 48 hours.

The implications of the present results are unclear, yet they raise several questions which should be investigated, particularly: 1) Would every-other-day O_3 exposures lead to desensitization to O_3 as has been demonstrated for consecutive days of exposure?[1-3,5,6,12]; and 2) If every-other-day exposures lead to desensitization, is the number of exposures required before desensitization develops the same or different than with consecutive-day exposures? The results also increase concern for the health and well-being of persons particularly responsive to O_3 exposure, since they are at increased risk of response not only with 2 consecutive days of O_3 exposure, but also if the two exposures are separated by 2 days. Further investigation into the duration of increased responsiveness to O_3 is warranted, as are similar investigations at lower O_3 levels.

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References

1. **Farrell, B.P., H.D. Kerr, T.J. Kulle, L.R. Sauder and J.L. Young:** Adaptation in Human Subjects to the Effects of Inhaled Ozone After Repeated Exposure. *Am. Rev. Respir. Dis. 119*:725-730 (1979).
2. **Folinsbee, L.J., J.F. Bedi and S.M. Horvath:** Respiratory Response in Man Repeatedly Exposed to Low Concentrations of Ozone. *Am. Rev. Respir. Dis. 121*:431-439 (1980).
3. **Folinsbee, L.J., J.F. Bedi, J.A. Gliner and S.M. Horvath:** *Concentration Dependence of Pulmonary Function Adaptation to Ozone.* In *The Biomedical Effects of Ozone and Related Photochemical Oxidants.* Edited by M.A. Mehlman, S.D. Lee and M.G. Mustafa. Princeton Junction, N.J.: Princeton Scientific Publishers, Inc., pp. 175-187. 1983.
4. **Hackney, J.D., W.S. Linn, D. Law, S. Karuza, H. Greenberg, R. Buckley and E. Pedersen:** Experimental Studies on Human Health Effects of Air Pollutants, III. *Arch. Environ. Health 30*:385-390 (1975).
5. **Horvath, S.M., J.A. Gliner and L.J. Folinsbee:** Adaptation to Ozone: Duration of Effect. *Am. Rev. Respir. Dis. 123*:832-837 (1982).
6. **Kulle, T.J., L.R. Sauder, H.D. Kerr, B.P. Farrell, M.S. Bermel and D.M. Smith:** Duration of Pulmonary Function Adaptation to Ozone in Humans. *Am. Ind. Hyg. Assoc. J. 43*:832-837 (1982).
7. **Linn, W.S., D.A. Medway, V.T. Anzar, L.M. Valencia, C.E. Spier, F.S. Tsao, D.A. Fischer and J.D. Hackney:** Persistence of Adaptation to Ozone in Volunteers Exposed Repeatedly for Six Weeks. *Am. Rev. Respir. Dis. 125*:491-495 (1982).
8. **Gliner, J.A., S.M. Horvath and L.J. Folinsbee:** Pre-Exposure to Low Concentration of Ozone Does Not Diminish the Pulmonary Function Response to Higher Ozone Concentrations. *Am. Rev. Respir. Dis. 127*:51-55 (1983).
9. **Bedi, J.F., L.J. Folinsbee, S.M. Horvath and R.S. Ebenstein:** Human Exposure to Sulfur Dioxide and Ozone: Absence of a Synergistic Effect. *Arch. Environ. Health 34*:233-239 (1979).
10. **Bedi, J.F., S.M. Horvath and L.J. Folinsbee:** Human Exposure to Sulfur Dioxide and Ozone in a High Temperature-Humidity Environment. *Am. Ind. Hyg. Assoc. J. 43*:26-30 (1982).
11. **Adams, W.C. and E.S. Schelegle:** Oxygen Toxicity Effects Consequent to Prolonged High Intensity Exercise in Trained Endurance Athletes. *J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 55*:805-812 (1983).
12. **Hackney, J.D., W.S. Linn, J.G. Mohler and C.R. Collier:** Adaptation to Short-Term Respiratory Effects of Ozone in Men Exposed Repeatedly. *J. Appl. Physiol. 43*:82-85 (1977).
13. **Golden, J., J.A. Nadel and H.A. Boushey:** Bronchial Hyperirritability in Healthy Subjects After Exposure to Ozone. *Am. Rev. Respir. Dis. 118*:287-294 (1978).
14. **Holtzman, M.J., J.H. Cunningham, J.R. Sheller, G.B. Irsigler, J.A. Nadel and H.A. Boushey:** Effects of Ozone on Bronchial Reactivity in Atopic and Nonatopic Subjects. *Am. Rev. Respir. Dis. 120*:1059-1067 (1979).
15. **Dimeo, M.J., M.G. Glenn, M.J. Holtzman, J.R. Sheller, J.A. Nadel and M.A. Boushey:** Threshold Concentration of Ozone Causing an Increase in Bronchial Reactivity in Humans and Adaptation With Repeated Exposures. *Am. Rev. Respir. Dis. 124*:245-248 (1981).
16. **Last, J., M. Jennings, L. Schwartz and C. Cross:** Glycoprotein Secretion by Trachael Explants Cultured From Rats Exposed to Ozone. *Am. Rev. Respir. Dis. 116*:695-703 (1977).
17. **Mustafa, M.G. and D. Tierney:** Biochemical and Metabolic Changes in the Lung With Oxygen, Ozone, and Nitrogen Dioxide Toxicity. *Am. Rev. Respir. Dis. 118*:1061-1090 (1978).
18. **Plopper, C.G., C.K. Chow, D.L. Dungworth, M. Brummer and T.J. Nemeth:** Effects of Low Level Ozone on Rat Lungs. II. Morphological Response During Recovery and Re-Exposure. *Exp. Mol. Pathol. 29*:400-411 (1978).

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